PATENT COOPERATION TREATY

# PCT

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference JPP183 | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| International application No. PCT/GB 03/00966 | International filing date *(day/month/year)* 07.03.2003 | Priority date *(day/month/year)* 07.03.2002 |
| International Patent Classification (IPC) or both national classification and IPC C12N3/00 | | |
| Applicant ROYAL HOLLOWAY UNIVERSITY OF LONDON, et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 02.10.2003 | 15.07.2004 |
| Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized Officer Rojo Romeo, E Telephone No. +49 89 2399-7321 |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/00966

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

**Description, Pages**

1-37 as originally filed

**Claims, Numbers**

1-30 received on 25.02.2004 with letter of 20.02.2004

**Drawings, Sheets**

1/14-14/14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   *(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 10, 12-17, 20, 21 |
| | No: | Claims | 1-9, 11, 18, 19, 22-30 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-30 |
| Industrial applicability (IA) | Yes: | Claims | 1-30 (see comment for claims 29 and 30) |
| | No: | Claims | |

2. Citations and explanations

   **see separate sheet**

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following documents cited in the International Search Report:

D1: WO 02 00232 A (MAXYGEN INC ;GOLDMAN STANLEY (US); WHALEN ROBERT G (US); LATHROP S) 3 January 2002 (2002-01-03)

1. Novelty (Art. 33(2) PCT)

D1 discloses recombinant spores expressing peptides. These spores are useful as therapeutic or prophylactic agents or vaccines against a broad spectrum of immunogens and bacterial and viral pathogens. The spores used can be viable or not (see page 11). The ways of delivery of the recombinant spores are respiratory, nasal, parenteral, and mucosal. It is contemplated to use one or several plasmids, thus giving the possibility to express several peptides (see pages 4-5, example 11). Fig. 4 discloses the spore surface display of a Yersinia pestis V antigen fused to the CotC spore coat protein of B. subtilis and a viral epitope exemplified by HA1. Fig. 12 is concerned with a fusion to CotV and Fig. 9-11 disclose the oral administration of the recombinant spores to mice to test for efficacy. Various fusions to spore coat proteins are contemplated (see page 22: CotC, CotG, CotD, etc.)

Claim 1 is now drawn as a first medical use. This is a product claim. For the purpose of the international examination, the terms for "use in" are to be read as "suitable for". The spores described in D1 (see e.g. example 9) are Bacillus spores displaying the Yersinia V antigen on the surface as a fusion protein with CotC. These spores were used for and are thus suitable for oral administration. Thus, D1 is novelty destroying for the subject-matter of claims 1-9, 11, 18, 19, 22-30.

In addition, Applicant's attention is drawn to the fact that these spores were also used for nasal administration and shown to provide a therapeutic effect using this way of administration (see Fig. 10: titer of around 10000 with V7 recombinant spores alone). A therapeutic use of "a Bacillus spore which is genetically modified with genetic code comprising at least one genetic construct encoding a therapeutic active compound and a targeting sequence or a vegetative cell protein" was therefore already known from prior art. A first medical use claim is thus not suitable.

When used orally, the recombinant spores disclosed in D1 do not lead to a significant

titre. The present set of claims does not contain any additional technical feature when compared to the disclosure of D1. No such technical feature is clearly recognisable in the description. An additional objection for lack of disclosure therefore arises (Art. 5 PCT).

D1 is thus novelty destroying for the subject-matter of claims 1-9, 11, 18, 19, 22-30.

2. Inventive step (Art. 33(3) PCT)

2.1 D1 already discloses the use of various antigens amongst which tetanus is found (page 62). The choice of a fragment of tetanus toxin fragment C or labile toxin B subunit is just an alternative choice of an antigen and does not show any inventive activity. Thus, claim 10 is not inventive. The same applies to the subject-matter of claims 12, 20 and 21.

2.2 In the absence of a surprising effect/advantage due to the choice of the specific proteins rrnO or oppA to construct the claimed fusion proteins when compared to already disclosed recombinant spores expressing similar fusion proteins with the same aims of providing e.g. vaccines and therapeutic compounds, the subject-matter of claims 13-17 does not show any inventive activity.

Consequently, claims 1-30 lack inventive step.

3. Industrial applicability (Art. 33(4) PCT)
For the assessment of the present claims 29 and 30 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4. Additional remarks
Applicant's attention is drawn to the fact that the present set of claims is very unclear and not representative of the subject-matter disclosed in the application as filed. Additional objections for lack of clarity, support by the specification and complete

disclosure of the invention are to be expected in the regional phase.

# CLAIMS

1. A Bacillus spore which is genetically modified with genetic code comprising at least one genetic construct encoding a therapeutically active compound and a targeting sequence or a vegetative cell protein for use in oral administration for therapeutic treatment.

2. A spore as claimed in Claim 1 characterised in that the therapeutically active compound is an antigen or a medicament or a precursor to an antigen or a medicament.

3. A spore as claimed in Claim 1 or Claim 2 characterised in that the gene construct is a chimeric gene..

4. A spore as claimed in any one of the preceding Claims characterised in that the genetic modification is accomplished by transformation of a mother cell using a vector containing the gene construct and then inducing the mother cell to produce spores as defined in any one of the preceding Claims.

5. A spore as claimed in any one of the preceding Claims characterised in that the gene construct is under the control of one or more of, each or independently, an inducible promoter, a promoter or a strong promoter or modified promoter.

6. A spore as claimed in Claim 5 characterised in that the gene construct has an enhancer element or an upstream activator sequence associated with it.

7. A spore as claimed in any one of the preceding Claims characterised in that the construct comprises an inducible expression system.

8. A spore as claimed in any one of the preceding Claims characterised in that the spore germinates in the duodenum and/or the jejunum of an intestinal tract of a human or animal body.

9. A spore as claimed in any one of the preceding Claims characterised in that the therapeutically active compound is an antigen which, in use, is adapted to elicit an immune response.

10. A spore as claimed in Claim 9 characterised in that the antigen is at least a fragment of tetanus toxin fragment C or labile toxin B sub unit.

11. A spore as claimed in any one of the preceding Claims characterised in that the protein is a protein that is expressed in the cell barrier.

12. A spore as claimed in any one of the preceding Claims characterised in that the protein is expressed all the time in a vegetative cell.

13. A spore as claimed in Claim 12 characterised in that the protein is OppA or rrnO.

14. A spore as claimed in any one of Claims 1 to 11 characterised in that the protein is expressed intermittently in a vegetative cell.

15. A spore as claimed in any one of Claims 1 to 10 characterised in that the protein is a soluble cytoplasmic vegetative cell protein.

16. A spore as claimed in Claim 15 characterised in that the protein is rrnO.

17. A spore as claimed in Claim 15 or Claim 16 characterised in that the genetic construct of the soluble cytoplasmic protein wholly or partially comprises a signal sequence.

18. A spore as claimed in any one of Claims 1 to 10 characterised in that the signal sequence is adapted to target the therapeutically active compound to a specific part of the vegetative cell.

19. A spore as claimed in Claim 18 characterised in that the signal sequence directs the therapeutically active compound for secretion (preferably active secretion, more preferably Type I, Type II or Type III secretion), or for post-translational processing by a vegetative cell (preferably glycosylation).

20. A spore as claimed in any one of the preceding Claims characterised in that the therapeutically active compound is an antigen precursor which is one or more enzymes capable of transforming a biological precursors, such that upon germination said one or more enzymes are expressed and synthesise one or more antigens by transformation of a said biological precursor.

21. A spore as claimed in Claim 20 characterised in that the biological precursor is a hormone, a steroid hormone, a painkiller or a pro-drug.

22. A spore as claimed in any one of Claims 1 to 19 wherein the therapeutically active compound is a medicament which is a protein, a vaccine or an endorphin.

23. A spore as defined in any one of the preceding Claims characterised in that it is for use in treatment of a medical condition, preferably the medical condition is inflammation, pain, a hormonal imbalance and/or an intestinal disorder.

24. A composition comprising at least two different spores as defined in any one of the preceding Claims characterised in that said at least two different spores express at least two different therapeutically active compounds.

25. A composition as defined in Claim 24 characterised in that the composition further comprises a pharmaceutically acceptable excipient or carrier.

26. A composition comprising a spore as defined in any one of claims 1 to 23 in association with a pharmaceutically acceptable excipient or carrier.

27. A composition as defined in any one of Claims 24 to 26 for use in treatment of a medical condition, preferably the medical condition is inflammation, pain, a hormonal imbalance and/or an intestinal disorder.

28. Use of a spore as defined in any one of claims 1 to 23 in the manufacture of a medicament for use in the treatment of a medical condition, preferably the medical condition is inflammation, pain, a hormonal imbalance and/or an intestinal disorder.

29. A method of medical treatment, which method comprises the steps of

a) administering a spore as defined in any one of claims 1 to 23 to a human or animal in need of medical treatment;

b) said spore germinating into a vegetative cell in the intestinal tract;

c) said vegetative cell expressing a therapeutically active compound for use in the medical treatment.

30. A method as claimed in Claim 29 characterised in that the spore is administered orally, intra-nasally or rectally.